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# ON THE EXISTENCE OF A DYNAMIC CRITICAL POINT BY USING WET MILLING ON (±) MODAFINIL

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**Abstract**

This study has been carried out on the molecular compound (±) modafinil, which exhibits five pure polymorphic forms (I, III, IV, V and VI). At P = 1 atm, irrespective of temperature and without any milling energy, Form I is the stable form. Therefore, the other polymorphic forms (III, IV, V and VI) are of monotropic character.

The steady states of (±) modafinil have been investigated as a function of wet milling parameters (milling intensity and water concentration). The results presented here suggest the existence of a dynamic critical point defined by Tc ≈ 40°C, P*c* ≈ 1 atm, Ic ≈ k R; R=50, Xc = 2% mass percent of water, respectively the critical: mean temperature, global pressure, milling intensity proportional to R and water composition (in mass percent)..

## Introduction

The (dry or wet) High Energy Milling (HEM) is a well known route to reach polymorphic forms, amorphous state, co-crystals or solvates and host-guest inclusions of molecular compounds [1-3].

Under external forces (e.g. irradiation or HEM), dynamic equilibrium can be far from thermodynamic equilibrium. In other words, these steady states do not correspond to the minima of the Gibbs free energy.

Under HEM, two processes exist: damage and recovery. When a dynamic equilibrium between damage and recovery is reached, a steady state is observed. That is to say the nature and the spatial distribution of the solid phase(s) do not evolve.

The nature of the steady state depends on several parameters. Different theories on the nature of these parameters have been proposed:

1. The momentum will be the control parameter [4]. The momentum, *M* associated to a single ball, is defined by the following formula (Eq. 1):

$$M = V_b * m_b \quad (1)$$

where $V_b$ stands for the ball velocity and $m_b$ stands for the mass of a ball.

2. The theory of the forced phases has been introduced by Martin [5]. This theory has been based on the analogies between phenomena observed under irradiation and the results obtained under HEM. Indeed, the flux of irradiation or the milling intensity could be considered as the external force. The mass of trapped powder was not taken into account by the original forced phase theory.

3. The third theory considers the mass of trapped powder between balls or between balls and the wall of the vial. This hypothesis has been introduced by Gaffet [6]. From this theory, several parameters have been introduced:

   - *The composition of the system*: In our case, it was the presence (or not) of solvent(s) but for instance it could be the composition in a second solute or in an excipient: i.e. co-grinding [7].

   - *Mean milling temperature*: Under HEM, two types of temperature exist:

     - The "local" temperature is the sudden rise in temperature during a shock. The peak temperature is difficult to measure directly because of microscopic and dynamic nature of the process [8]

     - The mean milling temperature corresponds to the rise in temperature inside the vial and could be monitored by a system of vial equipped with a thermal probe. The mean temperature is a function of the shock energy and the impact frequency.

       The kinetic of phase transition (e.g amorphisation) and the nature of the steady state depends on the mean milling temperature [9],

   - *Milling intensity*: The milling intensity (*I*) is defined as the momentum transferred by a ball to

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the unit mass of powder per unit time. It is defined by the following formula (Eq. 2):

$$I = (m_b * V_b * f)/m_p \quad (2)$$

where, $m_b$ = total mass of the balls, $V_b$ = maximum velocity of balls, $f$ = impact frequency, and $m_p$ = mass of the powder submitted to HEM

In so called 'local model' the milling intensity is applied to the volume of trapped powder [10]. According to the literature [6], in the case of planetary milling, the impact velocity and the shock frequency depend on the disk radius and the milling couple ($\Omega, \omega$) [$\Omega$ = velocity of disk, $\omega$ = velocity of vial]. If these parameters are constant, the milling intensity depends on the ratio -

$R = m_b / m_p$

Critical Point

The concept of critical point can be applied when upon modification of a physical parameter two well-separated phases continuously converge by changing their intensive properties and/or chemical parameters and finally collapse into a single phase. This single phase is called a hypercritical phase.

For example, in a unary phase diagram liquid/ vapour, the critical point is defined by the 'critical' temperature ($T_c$) and pressure ($P_c$). Above this point, there is the domain of the hypercritical fluid (this phase is neither a vapour nor a liquid but has a dual character). Furthermore, this transition is reversible.

For instance in binary systems, miscibility gaps associated or not with a monotectic invariant (e.g. Water – phenol system [11]) but also of a monotectoid invariant are illustrations of critical points in the liquid state but also in the solid state. In ternary systems as well, plait points are illustrations of this concept.

Similarly, under HEM, the existence of a dynamic critical point could be proposed if the four following conditions are fulfilled:

1. Below the critical point, two solid phases coexist as a dual steady state. Their physical and chemical properties converge as the parameters (I, T, P, X) approach the critical values.

2. At the critical point, the two phases collapse into a single phase

3. Above the critical point, the single phase shares properties with the former solid phases.

4. The phenomenon is reversible

As detailed above, under HEM, three parameters control the nature of the possible steady states: Milling intensity, mean temperature and the composition (in our case, presence of water). In this study, the influence of milling intensity (here, proportional to the number of balls) and water quantity on polymorphic transformations of (±) modafinil have been studied.

The polymorphism of (±) modafinil is presented in the section below.

(±) modafinil exhibits five polymorphic forms. The structures of Form III has been determined by using the DCP model on the crystal structure of Form I [12] and later on confirmed by single crystal X-ray diffraction (Table 1) [13]. At P = 1atm, whatever the temperature, Form I is the stable form and Form III the second best in terms of stability, but the difference in energy is quite small. Consistently, they exhibit a high degree of similarity highlighted by the DCP model. Without particular precaution, Form I and III are concomitant polymorphs [14].

As schematized in Fig. 1, the analysis of the structural similarities between Form I and Form III allowed us to identify that several stacking faults of $(002)A_{FormI}$, periodically repeated, lead to the local formation of Form III [15]. Conversely, repeated stacking fault in Form III could lead to domain of Form I.

**Table 1**. Crystallographic data of modafinil Form I and Form III at 20° C

| | a (Å) | b (Å) | c (Å) | β | density | Z' | Space group |
|---|---|---|---|---|---|---|---|
| Form I | 14.517 | 9,71 | 20.875 | 110.14° | 1.314 | 2 | $P2_1/a$ |
| Form III | 14.517 | 9,71 | 19.763 | 90° | 1.3035 | 2 | $Pna2_1$ |

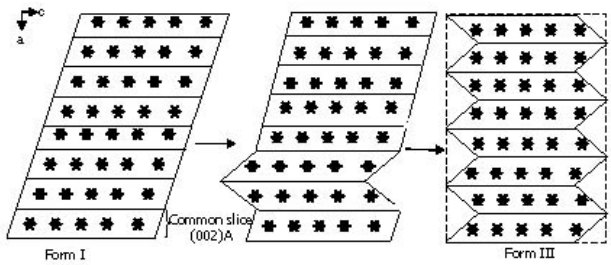


Figure 1. Structural relation between Form I and Form III and any possible intermediate of (±) modafinil

## Experimental

High Energy Milling Setup and Parameters

The planetary mill used is the Pulverisette 4 (P4) from Fritsch (Oberstein, Germany). This mill is composed of two vials (80ml) attached to a horizontal disk; the vial rotation speed and the disk rotation speed being independent.

As detailed below, the experiments were composed of three consecutive steps. At the end of each step, which lasted ten hours, the solid was analysed by means of X-Ray powder diffraction. The number of balls at every step has been optimized in order to obtain the best kinetics of solid–solid transition. The parameters that remained unchanged in all the experiments are:

- Mass of powder = 2.5g of (±)modafinil
- ($\Omega$, $\omega$) = (400,-400) rpm
- Milling duration for every step = 10 hours
- Balls and vials material = tungsten carbide (density = 14.7)
- Mass of a ball = 7.5g; and Diameter of a ball = 10 mm

Several experiments have been carried out: in a first series, dry milling has been applied and already reported [16]. In this study 'wet' milling conditions have been used and the average temperature was 40°C.

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## Results and Discussion

Results

The results of the wet milling experiments are reported in Table 2. X-ray powder diffraction (XRPD) patterns of the samples in these experiments are presented in the Figs. 2, 3 and 4.

**Table 2**: Results of milling with different amounts of water

| Step | R[1] | Number of balls[2] | Dry Milling[3] | Wet milling (% water) | | |
|---|---|---|---|---|---|---|
| | | | | 1% | 2% | 3% |
| Step 1 | 15 | 5 | defective Form III | I + III | I + III | defective Form I |
| Step 2 | 50 | 20 | $F_{com\ I,III}$ | $F_{com\ I,III}$ | $F_{com\ I,III}$ | $F_{com\ I,III}$ |
| Step 3 | 9 | 3 | $F_{com\ I,III}$ | $F_{com\ I,III}$ | I + III | defective Form I |

[1] $R = m_p/m_b$
[2] ball diameter (Ø) =10 mm
[3] 0% water

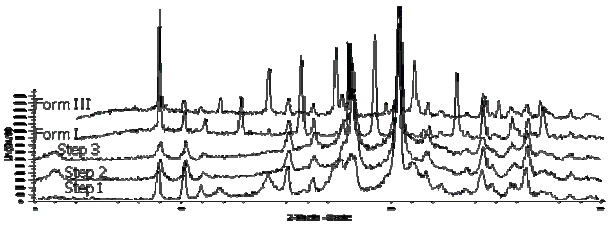


Figure 2. XRPD pattern of 'dry' milling

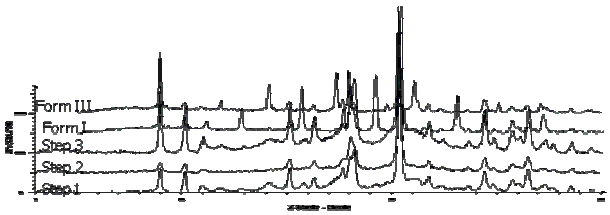


Figure 3. XRPD pattern of 'wet' milling (2% of water)

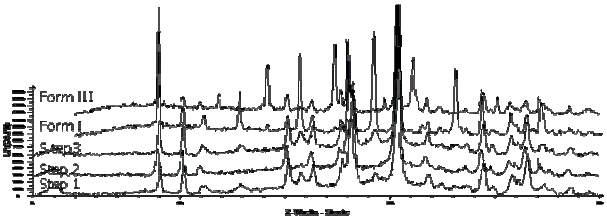


Figure 4. XRPD pattern of 'wet' milling (3% of water)

Discussion

Under HEM and whatever the quantity of water (up to 3 %mass), above the critical milling intensity, a new phase $F_{comI,III}$ is obtained. This phase exhibits only the common diffraction peaks between Form I and Form III. According to the literature [12], Form I and Form III exhibit a common slice $(002)A_{FI}$. The packing of this slice along c-axis determine the nature of the polymorphic form (Form I or Form III).

$F_{comI,III}$ is likely to correspond to a random stacking of this $(002)A_{FI}$ slice. With this hypothesis in hand, $F_{comI,III}$ could therefore correspond to some kind of smectic phase.

Whatever the analytical method (X-Ray powder diffraction, Raman spectroscopy, DSC, etc.), the exact nature of this phase remained unclear.

We are currently launching a study on the diffuse scattering background by using the Pair Distribution Function (PDF) analysis. This analytical method includes the simultaneous analysis of Bragg peaks and the background; it usually helps in defining partly disordered crystal structures and nano-crystalline powders. The access to the micro and local structures would be possible by combining PDF analysis, based on the X-Ray powder diffraction (or neutron diffraction), and Rietveld refinement.

The results lead to differentiate three different behaviors:

1. Quantity of water < 1% (mass)

At medium intensity (R=15), an inversion of the relative stability between Form I and Form III has been observed. This result confirms data obtained by using dry HEM. After a spell at R = 50 and return to R = 9, no reversibility from $F_{com\ I,III}$ into defective Form III has been detected even after prolonged milling (several days). Therefore with this concentration of water, the system remains out of dynamic equilibrium; there is no equilibrium between damage and recovery.

2. Quantity of water < 3%

At medium intensity (that is to say R=15), a mixture of defective Form I and defective Form III are in reversible dynamic equilibrium. After 10 hours under HEM with R=50,

$F_{com\ I,III}$ only is obtained. On return to lower milling energy R=9, $F_{com\ I,III}$ disappears to give back the former mixture of defective Form III and defective Form I in dynamic equilibrium. A striking analogy with thermodynamic critical point is then observed.

3. Quantity of water > 3%

At medium intensity, defective Form I has been observed. In this case, water prevents the transition from defective I into defective Form III. On return from R = 50 to R = 9, the transition from $F_{com\ I,III}$ into defective Form I has been observed.

The presence of water seems to control the nature of the steady state at medium milling intensity (defective Form I, defective Form III or mixture of the two). When milling intensity is reduced, if the water concentration is below 2% (mass percent), the transition towards less defective solids does not appear reversible even after several days of milling.

With 2 mass percent of water, $F_{com\ I,III}$ could be identified as a dynamic hypercritical phase, because when I is reduced from 50 to 9, the return to the dynamic equilibrium : *defective Form I ↔ defective Form III,* is re-observed and schematized in Fig. 5.

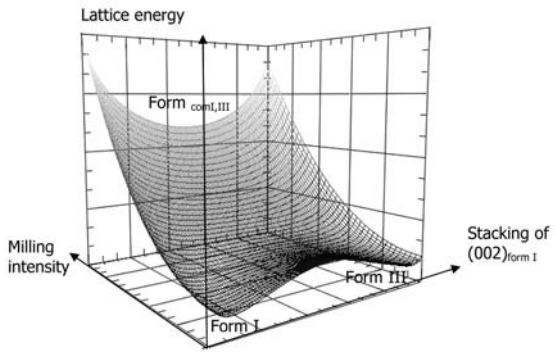


Figure 5. Schematic representation of the lattice energy vs. the milling intensity with 2% of water and the mode of stacking of the (002) slice

## Conclusions

Under HEM, the existence of a dynamic critical point could be proposed if the following four conditions are fulfilled:

- For I < Ic defective Form I and defective Form III coexist as two concomitant steady states in dynamic equilibrium.
- Two phases collapse into a single phase at I = Ic .
- Above the critical point, a unique phase exists and has a dual character.
- The phenomenon is reversible.

The behavior of (±) modafinil under HEM with 2% of water (mass percent) is the following:

- Whatever the initial variety of the starting material, after a sufficient period of milling, defective Form I and defective Form III coexist has long as the intensity of milling is below the threshold defined by R=50
- When R is set above 50, a single phase labeled $F_{com\ I,III}$ appears. This phase has the common structural features between Form I and Form III. It could be named as a 'dynamic hypercritical phase'.
- When the milling intensity is reduced to circa R = 9 , $F_{com\ I,III}$ splits back fast to a physical mixture of defective Form I and defective Form III in dynamic equilibrium.

If the water concentration is below 1%, defective Form III is the only phase which exists for R < 50 and $F_{com\ I,III}$ exists for R>50. No reversibility has been observed when R is dropped below 50; $F_{com\ I,III}$ remains unchanged; the system is out of dynamic equilibrium.

If the water concentration is above 3%, defective Form I is the only phase which exists for R < 50 and $F_{com\ I,III}$ exists for R>50. When R is set back below 50; defective Form I is the only phase again.

Therefore, it is only within a narrow window in water concentration (2% ± 0.5% mass) that the concept of dynamic critical point under HEM applies.

In the case of (±) modafinil ; this critical point could be defined by Tc ≈ 40°C, P*c* ≈ 1 atm, Ic ≈ k R; R=50, Xc = 2% mass percent of water, respectively the critical: mean temperature, global pressure, milling intensity proportional to R and water composition (in mass percent).

## Nomenclature

HEM: High Energy Milling

M: Momentum (g.m/s)

I: Milling intensity ($m^2/s$)

$m_b$: Global mass of balls (g)

$m_p$: Global mass of powder (g)

*f*: Impact frequency (counts/s)

Ω: Supporting disk speed (rpm)

$\omega$: Velocity of vial (rpm)

Tc: Critical temperature (°C)

Pc: Critical pressure (Pa)

R: $m_b/m_p$

PDF: Pair Distribution Function

Defective form: crystallized phase with broadened diffraction peaks

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